Association between thigh circumference and carotid intima-media thickening

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ABSTRACT

Association between thigh circumference and carotid intima-media thickening

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Objective: Currently, studies have reported relationships between the different anthropometric indices of obesity and risk for atherosclerosis. Specifically, there are few studies of the relationship between lower-body composition parameters such as thigh circumference and atherosclerosis. Therefore, this study aims to assess the association between thigh circumference and carotid intima-media thickness (IMT) as a marker of atherosclerosis.

Methods: This study used data from the Korean Genome and Epidemiology Study (KoGES)–Kangwha, a community-based prospective cohort study with 779 men, 393 premenopausal, and 839 postmenopausal women, without history of stroke, angina, and cancer. Maxima of carotid IMT (CIMT) measured by ultrasonography were used as continuous variables. CIMT thickening was defined when CIMT $\geq$ 1.0 mm. Independent association between thigh, waist circumference, and waist-to-thigh ratio (WTR) and CIMT by sex and menopause status was assessed by cross-sectional and prospective analysis.

Results: Thigh circumference at baseline was inversely associated with change of CIMT even after adjustment for potential confounders such as baseline age, body mass index, waist circumference, systolic blood pressure, ratio of total cholesterol to high-density lipoprotein, alcohol intake, regular exercise, and follow-up period in premenopausal women (standardized β for CIMT = –0.154, $p = 0.013$) and postmenopausal women (standardized β for CIMT = –0.153, $p < 0.001$). But there is no significant association between thigh circumference and change of CIMT in men (standardized β for CIMT = –0.070, $p = 0.166$). The odds ratio (OR) for having CIMT thickening among baseline without CIMT thickening that decreased per 5 cm of thigh circumference at baseline was 1.74 (95% CI = 1.28–2.35) in postmenopausal women when adjusted for potential confounds, but not significant in men (OR = 0.95, 95% CI = 0.69–1.32) and premenopausal women (OR = 1.22, 95% CI = 0.82–1.82). Also, the OR for having CIMT thickening (OR =

1.58, 2.44, and 2.80, respectively; p for trend = 0.012) increased with decreasing quartile of thigh circumference. This trend was not shown in men or premenopausal women.

Conclusion: In postmenopausal women, a low thigh circumference seems to be associated with an increased risk of CIMT thickening. These results suggest that measure of thigh circumference might be a new anthropometric marker of early identification of individuals at an increased risk of atherosclerosis.

Key words: Thigh circumference, carotid intima-media thickness, atherosclerosis, menopause

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I. INTRODUCTION

1. Background

Obesity is a public health problem of increasing prevalence worldwide (Flegal et al. 2012; McLellan 2002; Ogden et al. 2014). Prospective epidemiological studies have observed a J- or U-shaped association between body mass index (BMI) and cardiovascular disease (CVD) morbidity and mortality, suggesting that both a low and a high BMI are associated with death (Ajani et al. 2004; Berrington de Gonzalez et al. 2010). Also, alternative abdominal obesity indices such as waist circumference and hip circumference and upper versus lower fat localization such as waist-to-hip ratio and waist-to-thigh ratio have been suggested to be predictive of coronary heart disease and vascular events such as stroke, myocardial infarction and cardiac death (de Koning et al. 2007; Ducimetiere and Richard 1988; Klein et al. 2007; Seidell et al. 2001). In contrast, leg muscle mass and peripheral adiposity might offer protection from atherosclerosis. Previous studies have shown that peripheral adiposity is inversely associated with markers of atherosclerosis such as aortic calcifications, coronary angiography score and arterial stiffness (Ferreira et al. 2004; Hara et al. 2004; Tanko et al. 2003).

Carotid intima-media thickness (IMT) is a validated noninvasive biomarker of the anatomic extent of atherosclerotic vascular disease and was shown to independently predict CVD (Bots et al. 1997; Chambless et al. 1997; Hodis et al. 1998; O'Leary et al. 1999; Tang et al. 2000). Atherosclerosis starts with focal thickening of the intima. During progression of the atherosclerosis, the arterial wall is changed by thickening of the intima and media. A systematic review and meta-analysis from 37,197 participants showed the association between carotid IMT and the relative risk for myocardial infarction and stroke. From this study, the age- and sex- adjusted relative risk of myocardial infarction was 1.15 (95%CI 1.12–1.17) per 0.1 mm carotid IMT difference and the age- and sex- adjusted relative risk of stroke was 1.18 (95% CI 1.16–1.21) (Lorenz et al. 2007). Previous studies have shown that men had higher carotid IMT than women, but predictors of early carotid atherosclerosis were similar across sexes (Sinning et al. 2011).

Currently, the association of carotid IMT with body composition parameters and fat distribution has been investigated. Indeed, several studies have reported that carotid IMT is associated with anthropometric markers of abdominal obesity (De Michele et al. 2002; Kato et al. 2010; Lakka et al. 2001; Park et al. 2010; Reed, Dwyer and Dwyer 2003; Takami et al. 2001). However, there are few studies of the relationship between lower body anthropometric parameters such as thigh circumference and thigh muscle-mass area and carotid IMT (Heitmann and Frederiksen 2009; Kato et al. 2010). In addition, association between thigh circumference and carotid IMT according to sex and menopause status has not been assessed.

2. Objective

The purpose of this study was to assess the association between thigh circumference and carotid IMT as a marker of atherosclerosis.

Specifically,

(1) To assess baseline thigh circumference with respect to change in carotid IMT

(2) To assess the association between thigh circumference and occurrence of carotid IMT thickening according to sex and menopause status

II. MATERIALS AND METHODS

1. Study participants

Subjects in the present study are participants in the Korean Genome and Epidemiology Study (KoGES)–Kangwha, a community-based prospective cohort study to assess cardiovascular diseases through the use of questionnaires, physical examinations, various types of biomarkers and DNA analysis. KoGES–Kangwha invited to participate all adults who resided in rural areas of Kangwha Island, Incheon, South Korea. Demographic shifts are infrequent in this area and the population can be followed long term.

The baseline survey, carried out from 2006 to 2011, included 4,899 adults aged 35 – 88 years. All study participants were invited to the first follow-up survey (2008 – 2012; follow-up period of 2.6years), of whom 2,404 (49.1%) attended. Of the 2,404 participants, 393 participants were excluded from the present analysis because of at least one of the following reasons: absence of carotid IMT measurement (n = 270), previously diagnosed of stroke, angina, and cancer (n = 105), missing anthropometric measurements (n = 10), and missing blood tests (n = 8). Finally, 2,011 participants (779 men and 1,232 women) were eligible for this study (figure 1).

All participants in this survey signed an informed consent. The study protocol was approved by the Institutional Review Board of

Yonsei University Health System (4-2004-0105, 4-2006-0101, 4-2008-0135, 4-2009-0270, 4-2010-0272, 4-2011-0274 and 4-2012-0278) and monitored by the Human Research Protection Center of Severance Hospital, Yonsei University Health System.

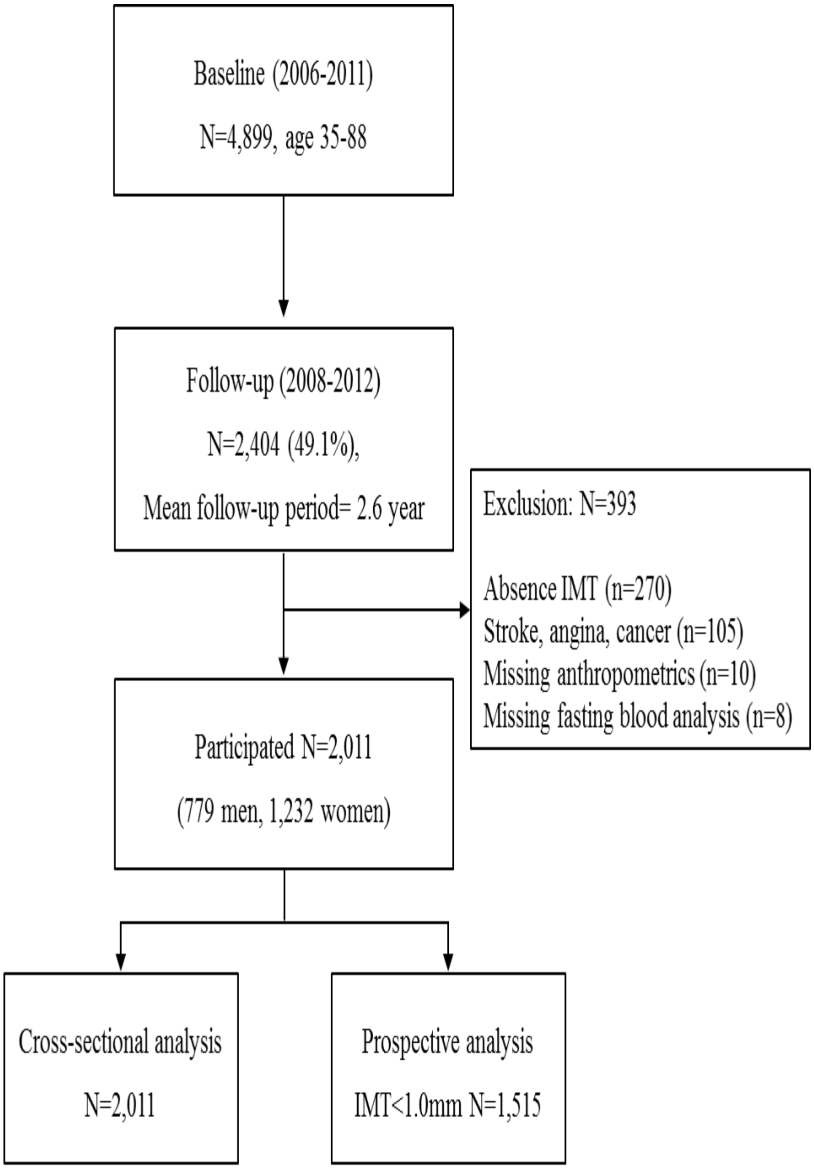


Figure 1. Flowchart of the selection criteria for the final study population

2. Measurements

A. Questionnaire

At baseline and at the follow-up examination, study participants completed a standardized questionnaire that was used to collect data on demographics, personal medical history, current medication, cigarette smoking, alcohol consumption, physical activity, parity and menopause status (for women). Interviews were conducted face-to-face by trained staff. Personal history of hypertension, diabetes mellitus, stroke, myocardial infarction, angina, cancer and others were obtained. Participants were asked if they continually took medicine for at least three months, and if the answer was affirmative, the name of medicine taken and duration of medication were recorded. Current smokers were defined as those who had smoked more than 100 cigarettes in a life time and reported presently smoking. Former smokers were those who had smoked greater than 100 cigarettes in a life but had not smoked recently and those who had smoked fewer than 100 cigarettes were defined as never smoker. The question about alcohol consumption consisted of three responses: never drinker, current drinker and former drinker. Participants were asked whether they regularly exercise. If they answered “yes,” they were asked to report the average frequency of exercise in a week and the average duration of exercise. For women, they were asked to report age of menarche, number of pregnancies, the first time of pregnancy, the number of live births, the time of first delivery. And they were asked to report the history of feeding breast, abortion, gestational diabetes, hysterectomy, menopause and taking a contraceptive pill.

B. Anthropometrics

Height, Weight and Body mass index

Standing height was measured to the nearest 0.1 cm on a stadiometer and body weight was measured to the nearest 0.1kg on a digital scale (Seca 763; SECA, Hamburg, Germany) while wearing underwear. The participant moved or removed hair ornaments from the top of the head in order to measure stature properly. The participant stood on the floor with the heels of both feet together and the toes pointed slightly outward at approximately a 60^{o} angle. The position of the heels, the buttocks, shoulder blades and the back of the head were checked for contact with the vertical backboard. Once correctly positioned, the participant took a deep breath and the headboard was lowered and positioned firmly on top of the head with sufficient pressure to compress the hair. When the participant was properly positioned, the height and weight were recorded by the examiners. Body mass index was calculated by dividing weight (kg) by the square of height (m^2).

Waist, Thigh Circumferences and Waist-to-thigh ratio

Waist and thigh circumferences were measured by trained examiners, when the participant stood with feet together, weight evenly distributed on both feet and opened his/her arms slightly. Waist circumference was measured to the nearest 0.1 cm around 2.0 cm below the umbilicus at the end of a normal expiration. Thigh circumference was measured when the participant stood with most of the weight on the left leg with the right leg forward, knee slightly flexed and soles of both feet flat on the floor. The circumference of mid-thigh (midpoint between anterior iliac crest and the proximal border of patella) was measured to the nearest 0.1 cm. All the circumferences were measured using a standard tape (Seca 200, SECA, Hamburg, Germany), when the tape was rested firmly on the skin without compressing it. Waist-to-thigh ratio (WTR) was calculated as the ratio of the waist and thigh circumferences.

C. Blood pressure

Blood pressure (BP) was measured by an automatic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, Waukesha, WI, USA). Before blood pressure measurements were acquired, participants were seated to rest in the room for at least five minutes. After rest, an appropriately sized cuff was applied snugly around the right upper arm at the heart level. Appropriate cuff size was chosen for each participant according to the mid-arm circumference. Two readings with at least five min interval were obtained and averaged to determine systolic and diastolic blood pressures for each individual. If the two readings differ by more than 10 mmHg, additional readings were obtained and the last two readings were averaged.

D. Laboratory test

Blood samples were taken after at least an eight hour fast. Total cholesterol, high density lipoprotein cholesterol (HDL-C), triglyceride, fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) were measured by enzymatic methods analyzers (ADVIA 1650; Bayer Corp, Tarrytown, NY, USA).

E. Carotid intima-media thickness

A trained sonographer performed all ultrasound examinations on subjects in supine position with the head slightly extended and turned to the opposite direction of the carotid artery being studied. Carotid intima-media thickness were measured in the left and right common carotid arteries using high-resolution B-mode ultrasonography (SSAD-3500SV; Aloka, Tokyo, Japan) using a 7.5-MHz linear transducer. A sonographer scanned the left and right common carotid arteries, the carotid bulb and the proximal portion of the internal and external carotid arteries in two planes (anterior oblique and lateral views) and then focused on the interfaces required to measure carotid IMT as well as on any areas of focal plaque. Carotid IMT was measured at the far wall of both common carotid arteries about 20 mm proximal from the carotid bulb. The distance between the leading edge of first and the second echogenic line was obtained using IMT software (Intima scope; Media Cross Co. Ltd, Tokyo, Japan). For the outcome variable, the CIMT was defined as the highest value among both carotid IMT and CIMT thickening was defined as CIMT > 1.0 mm.

3. Statistical analysis

All analyses were performed by SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and all analysis were two-sided and p values < 0.05 were regarded as statistically significant. Continuous variables were described as mean ± standard deviation (SD, for normally distributed variables) or as medians [interquartile range] (for skewed variables). Categorical variables were described as numbers (percentages) using chi-squared statistical tests. All analyses were performed separately in men, premenopausal, and postmenopausal women.

In cross-sectional analysis using baseline data, the correlation between CIMT with demographic and clinical factors including thigh circumference, where indicated, were evaluated by Pearson's correlation or Spearman's rank correlation as appropriate, after adjustment for age. In prospective analyses, changes in CIMT and thigh circumference were computed as the difference between baseline and follow-up values. The association of baseline thigh circumference with follow-up CIMT and change in CIMT were studied with multivariable regression analyses adjusted for baseline age, BMI, waist circumference (only thigh analysis), systolic BP, total cholesterol / HDL cholesterol ratio, alcohol intake, exercise, and follow-up period. The logistic regression analysis to assess the risk for CIMT thickening as a decrease of 5 cm of thigh circumference and 10 cm of waist circumference and WTR 0.1 unit was also adjusted for baseline age, BMI, waist circumference (only thigh analysis), systolic BP, total cholesterol / HDL cholesterol ratio, alcohol intake, exercise and follow-up period. To assess whether the association between thigh circumference per 5 cm decrease and CIMT thickening differed by baseline characteristics, stratified analyses by sex, age, smoking status, and exercise were adjusted for confounding factors. Additionally, we studied possible non-linear associations between thigh circumference and CIMT thickening by dividing the data into quartiles according to baseline thigh circumference.

III. RESULTS

1. Characteristics of men, premenopausal and postmenopausal women

Baseline values in general characteristics of men, premenopausal and postmenopausal women are presented in Table 1. This study comprised a baseline of 779 men with a mean age 56.5 years, 393 premenopausal women with 46.7 years and 839 postmenopausal women with 58.0 years.

In men, significant increases were observed in thigh circumference (IRQ, 0.1 [–2.4, 3.0] cm) and CIMT (IRQ, 0.04 [–0.06, 0.15] mm). Two hundred forty-two subjects (31.1%) were current smokers, 486 (62.4%) were current drinkers, and 302 (38.8%) were regular exercisers at baseline. In premenopausal women, significant increases were observed in thigh circumference (IRQ, 1.1 [–1.5, 3.8] cm) and CIMT (IRQ, 0.03 [–0.07, 0.13] mm). Six subjects (1.5%) were current smokers, 141 (35.9%) were current drinkers, and 143 (36.4%) were regular exercisers at baseline. In postmenopausal women, significant increases were observed in thigh circumference (IRQ, 0.7 [–2.0, 3.5] cm) and CIMT (0.05 IRQ, 0.04 [–0.06, 0.15] mm). Eighteen subjects (2.2%) were current smokers, 191 (22.8%) were current drinkers, and 277 (33.0%) were regular exercisers at baseline.

Table 1. Baseline characteristics of subjects

Variable	Men (n=779)	Premenopausal women (n=393)	Postmenopausal women (n=839)
Mean ± SD, (median [25%, 75%])			
Age, years	56.5 ± 8.1	46.7 ± 3.9	58.0 ± 6.3
BMI, kg/m^2	24.4 ± 2.8	24.6 ± 3.5	24.9 ± 3.1
Waist circumference, cm	86.9 ± 7.2	85.2 ± 8.4	88.2 ± 8.4
Waist-to- thigh ratio (WTR)	1.78 ± 0.15	1.72 ± 0.19	1.84 ± 0.19
Systolic BP, mmHg	122.3 ± 16.6	113.3 ± 16.6	120.5 ± 17.8
Diastolic BP, mmHg	78.3 ± 9.9	70.3 ± 10.0	72.9 ± 10.1
Total cholesterol, mmol/L	191.4 ± 32.2	188.8 ± 32.6	204.9 ± 36.0
HDL-C, mg/dl	41.0 ± 9.6	44.7 ± 10.1	43.9 ± 10.1
Triglycerides, mg/dl	129 [92, 191]	96 [72, 142]	120 [87, 161]
Total cholesterol/HDL-C ratio	4.86 ± 1.15	4.38 ± 1.03	4.83 ± 1.14
Fasting glucose, mg/dl	98.7 ± 21.8	91.6 ± 17.7	95.1 ± 18.7
AST, IU/l	24 [21, 29]	19 [17, 22]	22 [19, 26]
ALT, IU/l	24 [18, 32]	16 [13, 20]	19 [16, 25]
GGT, IU/l	28 [19, 48]	13 [10, 18]	15 [12, 22]
Number (%)			
Smoking (≥100 cigarettes)	242 (31.1)	6 (1.5)	18 (2.2)
Drinking (≥1 time/month)	486 (62.4)	141 (35.9)	191 (22.8)
Regular exercise (≥1time/week)	302 (38.8)	143 (36.4)	277 (33.0)
Thigh circumference, cm			
Baseline	48.9 ± 4.4	49.7 ± 4.9	48.3 ± 4.5
Follow-up	49.2 ± 4.5	50.7 ± 4.5	49.0 ± 4.6
Change	0.1 [-2.4, 3.0]*	1.1 [-1.5, 3.8]**	0.7 [-2.0, 3.5]**
CIMT, mm			
Baseline	0.963 ± 0.274	0.818 ± 0.187	0.913 ± 0.209
Follow-up	0.994 ± 0.245	0.845 ± 0.145	0.957 ± 0.226
Change	0.04 [-0.06, 0.15]*	0.03 [-0.07, 0.13]*	0.05 [-0.06, 0.15]**

Data are expressed as means ± SD, median [25%, 75%], number (%) and * <.05; **<0.001
Abbreviations: BMI; body mass index calculated as weight in kilograms divided by height in meters squared, Waist; waist circumference, BP; blood pressure, HDL-C; high-density lipoprotein cholesterol, AST; aspartate aminotransferase, ALT; alanine aminotransferase, GGT; gamma glutamyl transferase, Thigh; Thigh circumference, CIMT; carotid intima-media thickness.

2. Correlation coefficients between waist, thigh circumference, WTR, and other variables for CIMT at baseline and change

Tables 2 and 3 present the correlations between baseline CIMT and change of CIMT and other variables using Pearson’s correlation or Spearman’s rank correlation coefficients. In men, the baseline CIMT had no significant correlations with thigh circumference. In premenopausal women, the baseline CIMT had significant correlations with thigh circumference ($r = 0.125$, $p = 0.013$). Change in CIMT had significant correlations with WTR ($r = 0.120$, $p = 0.018$) (Table 3). In postmenopausal women, baseline CIMT had significant correlations with waist circumference ($r = 0.083$, $p = 0.016$), and thigh circumference ($r = 0.089$, $p = 0.010$). Change in CIMT had significant correlations with thigh circumference ($r = –0.090$, $p = 0.009$) and WTR ($r = 0.111$, $p = 0.001$)

Table 2. Correlation between waist, thigh circumference, WTR, and other variables with CIMT at baseline.

Variable	Age-adjusted					
	Men		Premenopausal women		Postmenopausal women	
	r	*p*	r	*p*	r	*p*
BMI	0.022	0.542	0.089	0.077	0.066	0.056
Waist circumference	0.018	0.614	0.091	0.072	**0.083**	**0.016**
Thigh circumference	0.032	0.366	**0.125**	**0.013**	**0.089**	**0.010**
WTR	-0.018	0.618	-0.032	0.529	0.000	0.989
Systolic BP	0.085	0.017	0.184	<.001	0.194	<.001
Diastolic BP	-0.006	0.869	0.187	<.001	0.091	0.008
Total cholesterol	0.064	0.075	0.030	0.550	0.069	0.046
HDL-C	-0.080	0.025	-0.147	0.004	-0.058	0.093
Triglycerides	0.017	0.637	0.105	0.037	0.027	0.438
Total cholesterol/HDL-C ratio	0.138	<.001	0.168	0.001	0.111	0.001
Fasting glucose	0.004	0.903	0.080	0.114	0.099	0.004
AST	0.011	0.753	-0.002	0.976	-0.011	0.751
ALT	0.050	0.164	0.087	0.086	0.020	0.565
GGT	-0.035	0.329	0.065	0.196	0.078	0.024

Table 3. Correlation between waist, thigh circumference, WTR, and other variables with change of CIMT.

Variable	**Age- & follow-up period-adjusted**					
	Men		**Premenopausal women**		**Postmenopausal women**	
	r	*p*	r	*p*	r	*p*
BMI	0.040	0.271	0.022	0.669	0.000	1.000
Waist circumference	0.040	0.269	0.050	0.320	0.022	0.533
Thigh circumference	-0.007	0.844	-0.085	0.094	**-0.090**	**0.009**
WTR	0.052	0.149	**0.120**	**0.018**	**0.111**	**0.001**
Systolic BP	0.015	0.675	-0.005	0.926	-0.004	0.900
Diastolic BP	0.045	0.211	-0.012	0.819	0.020	0.569
Total cholesterol	0.003	0.938	0.020	0.693	-0.038	0.271
HDL-C	-0.001	0.969	0.047	0.351	0.040	0.247
Triglycerides	0.030	0.403	-0.005	0.926	-0.004	0.914
Total cholesterol/HDL-C ratio	-0.018	0.608	-0.042	0.407	-0.068	0.049
Fasting glucose	0.057	0.110	-0.038	0.453	-0.016	0.640
AST	-0.048	0.180	0.056	0.273	-0.032	0.361
ALT	-0.025	0.490	0.010	0.849	-0.015	0.667
GGT	0.050	0.164	-0.018	0.725	0.001	0.987

3. Association between waist, thigh circumference, and WTR for CIMT at baseline and change

Tables 4 and 5 present the results of the multiple linear regression analysis on associations between waist, thigh circumference, and WTR and CIMT at baseline and at change. In men, baseline and change CIMT do not have significant association with thigh circumference when adjusted for all potential confounders. In premenopausal women, baseline CIMT was significantly associated with thigh circumference (S (ß) = 0.143, p = 0.016) when adjusted for all potential confounders. Change of CIMT is significantly inversely associated with thigh circumference (S (ß) = -0.154, p = 0.013) and has a positive association with WTR (S (ß) = 0.127, p = 0.017) when adjusted for all potential confounders. In postmenopausal women, baseline CMT was significantly associated with thigh circumference (S (ß) = 0.100, p = 0.016) when adjusted for all potential confounders. Change of CIMT has a significant inverse association with thigh circumference (S (ß) = –0.153, p = < .001) and positive association with WTR (S (ß) = 0.133, p = < .001) when adjusted for all potential confounders.

Table 4. Cross-sectional association between waist, thigh circumference, and WTR and CIMT.

Variable	Baseline CIMT					
	Men		Premenopausal women		Postmenopausal women	
	S (ß)*	*p*	S (ß)*	*p*	S (ß)*	*p*
Unadjusted						
Waist circumference	-0.014	0.695	**0.111**	**0.027**	**0.120**	**<.001**
Thigh circumference	**-0.077**	**0.033**	**0.117**	**0.020**	0.054	0.118
WTR	0.063	0.077	-0.005	0.918	**0.069**	**0.046**
Model 1						
Waist circumference	0.000	0.996	0.054	0.517	0.078	0.143
Thigh circumference	0.031	0.506	0.105	0.078	0.076	0.071
WTR	-0.022	0.538	-0.055	0.284	-0.012	0.730
Model 2						
Waist circumference	-0.044	0.474	0.027	0.743	0.069	0.187
Thigh circumference	0.058	0.220	**0.143**	**0.016**	**0.100**	**0.016**
WTR	-0.054	0.133	-0.083	0.106	-0.034	0.337

*S (ß) displays the standardized regression coefficients

Model 1 adjusted for baseline age, BMI, waist circumference (only thigh analysis)

Model 2 adjusted for baseline age, BMI, waist circumference (only thigh analysis), systolic BP, total cholesterol/HDL-C ratio, alcohol intake, and regular exercise.

Table 5. Prospective association between waist, thigh circumference, and WTR and CIMT change.

Variable	CIMT Change					
	Men		Premenopausal women		Postmenopausal women	
	S (ß)*	*p*	S (ß)*	*p*	S (ß)*	*p*
Unadjusted						
Waist circumference	0.039	0.281	0.050	0.319	0.029	0.399
Thigh circumference	-0.006	0.861	-0.073	0.150	**-0.095**	**0.006**
WTR	0.050	0.168	**0.107**	**0.034**	**0.120**	**<.001**
Model 1						
Waist circumference	0.022	0.732	0.091	0.280	0.054	0.327
Thigh circumference	-0.059	0.233	**-0.144**	**0.017**	**-0.140**	**0.001**
WTR	0.047	0.204	**0.122**	**0.020**	**0.119**	**0.001**
Model 2						
Waist circumference	0.034	0.608	0.095	0.258	0.063	0.258
Thigh circumference	-0.070	0.166	**-0.154**	**0.013**	**-0.153**	**<.001**
WTR	0.060	0.123	**0.127**	**0.017**	**0.133**	**<.001**

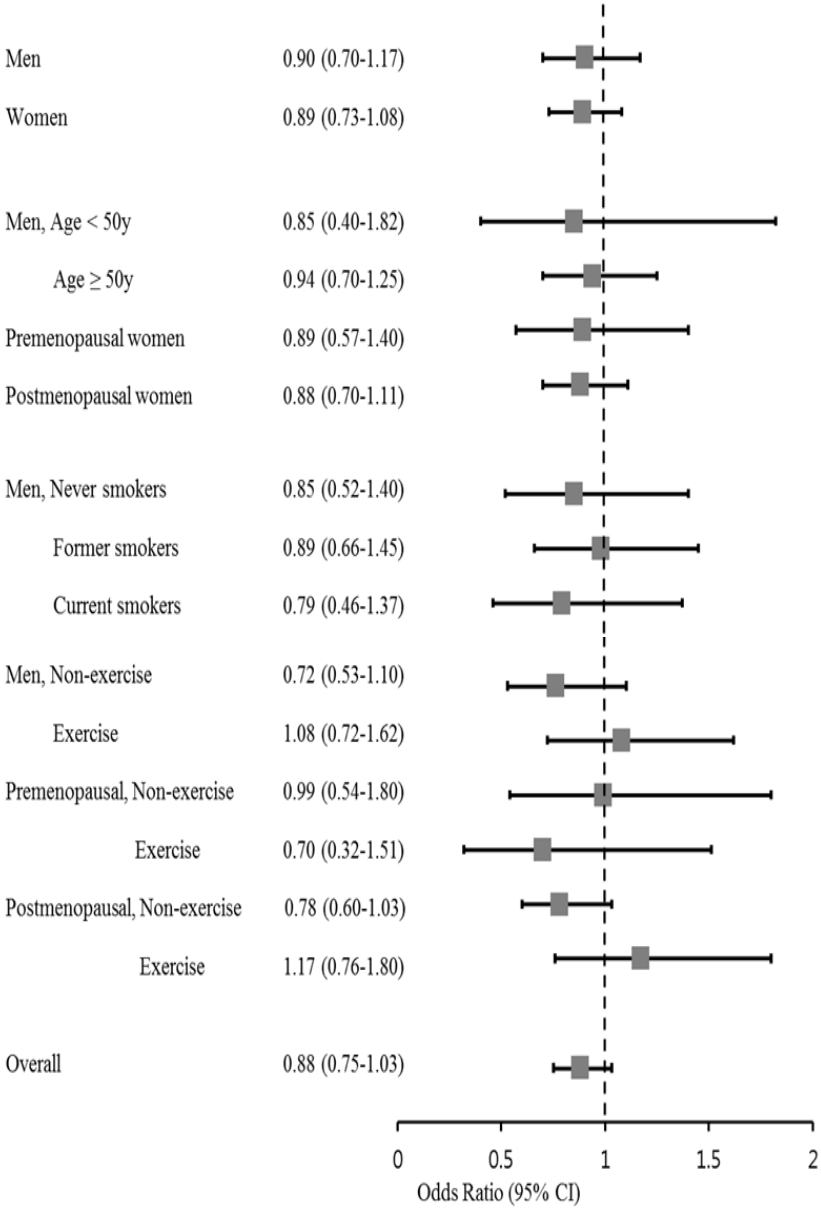
*S (ß) displays the standardized regression coefficients

Model 1 adjusted for baseline age, BMI, waist circumference (only thigh analysis)

Model 2 adjusted for baseline age, BMI, waist circumference (only thigh analysis), systolic BP, total cholesterol/HDL-C ratio, alcohol intake, and regular exercise.

4. Association between thigh circumference and CIMT thickening according to baseline characteristics

Figure 2 shows the results of stratified analysis for baseline characteristics in relation to CIMT thickening per 5 cm decrease of thigh circumference. The baseline characteristics were not significantly associated with CIMT thickening per 5 cm decrease of thigh circumference in when fully adjusted for confounding effects.



Adjusted for age, BMI, waist circumference, systolic BP, total-C/HDL-C ratio, alcohol intake and regular exercise

Figure 2. Cross-sectional association between thigh circumference and CIMT thickening according the baseline characteristics

5. Association between waist, thigh circumference, and WTR for CIMT thickening among baseline without CIMT thickening

Table 6 shows the risk of occurrence of CIMT thickening per unit of waist, thigh circumference, and WTR at baseline from among the baseline without CIMT thickening. CIMT thickening was presented using increased CIMT at follow-up. At this analysis, only in postmenopausal women, the risk of CIMT thickening was significantly increased as 5 cm increase of thigh circumference (OR = 1.42, 95% CI = 1.13–1.78) and as 0.1 increase of WTR (OR = 1.28, 95% CI = 1.16–1.42). These results remained significant (thigh circumference; OR = 1.74, 95% CI = 1.28–2.35 and WTR; OR = 1.21, 95% CI = 1.08–1.35) even after adjusting all potential confounding variables.

Table 6. Prospective association between baseline waist, thigh circumference, and WTR and CIMT thickening at follow-up.

(People with CIMT thickening <1.0mm at baseline)

	No. (%) of case	**Odds ratio (95% confidence interval) for CIMT thickening**		
		Unadjusted	**Model 1**	**Model 2**
Men	128/530 (24.2)			
Waist (per 10 cm increase)		1.24 (0.93-1.66)	0.98 (0.58-1.65)	0.92 (0.54-1.58)
Thigh (per 5 cm decrease)		0.97 (0.78-1.21)	1.01 (0.74-1.39)	0.95 (0.69-1.32)
WTR (per 0.1 increase)		1.07 (0.93-1.23)	0.99 (0.86-1.14)	0.96 (0.82-1.11)
Premenopausal women	41/351 (11.7)			
Waist (per 10 cm increase)		1.24 (0.84-1.81)	1.14 (0.59-2.22)	1.13 (0.57-2.22)
Thigh (per 5 cm decrease)		0.98 (0.71-1.36)	1.21 (0.82-1.79)	1.22 (0.82-1.82)
WTR (per 0.1 increase)		1.05 (0.90-1.22)	1.06 (0.91-1.25)	1.06 (0.90-1.25)
Postmenopausal women	152/634 (24.0)			
Waist (per 10 cm increase)		**1.29 (1.03-1.62)**	1.13 (0.78-1.64)	1.11 (0.76-1.61)
Thigh (per 5 cm decrease)		**1.42 (1.13-1.78)**	**1.76 (1.30-2.37)**	**1.74 (1.28-2.35)**
WTR (per 0.1 increase)		**1.28 (1.16-1.42)**	**1.21 (1.09-1.36)**	**1.21 (1.08-1.35)**

Model1 adjusted for baseline age, BMI, waist (only TC analysis), CIMT and follow-up period

Model2 adjusted for baseline age, BMI, waist (only TC analysis), CIMT, follow-up period, systolic BP, total-C/HDL-C ratio, alcohol intake, and regular exercise

6. CIMT thickening at follow-up by quartile of thigh circumference at baseline among baseline without CIMT thickening

Table 7 shows the risk of occurrence CIMT thickening by quartile of thigh circumference at baseline from among the baseline without CIMT thickening. OR of CIMT thickening for postmenopausal women were statistically significant compared with individuals with a highest quartile of thigh circumference. Also, OR for having CIMT thickening (OR = 1.58, 2.44, and 2.80, respectively; p for trend = 0.012) increased with decreasing quartile of thigh circumference. This trend was not observed in men or premenopausal women.

Table 7. Prospective association between quartile of baseline thigh circumference and CIMT thickening at follow-up.

(People with CIMT thickening <1.0mm at baseline)

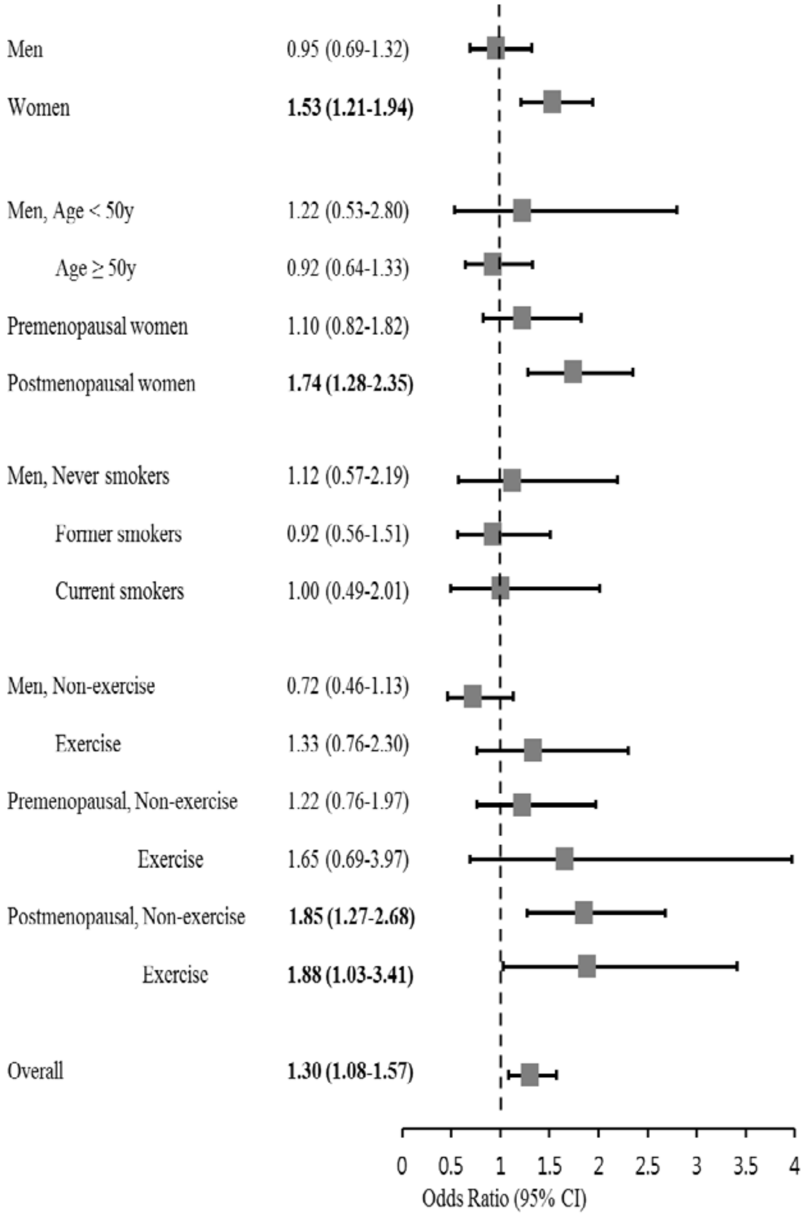
Variable	No. (%) of case	Odds ratio (95% confidence interval) for CIMT thickening		
		Unadjusted	Model 1	Model 2
Men				
Q4 (≥51.7, mm)	34/136 (25.0)	ref	ref	ref
Q3 (48.5-51.6, mm)	32/132 (24.2)	0.96 (0.55-1.67)	1.15 (0.61-2.16)	1.08 (0.57-2.06)
Q2 (46.3-48.5, mm)	28/131 (21.4)	0.82 (0.46-1.44)	0.94 (0.48-1.84)	0.91 (0.46-1.79)
Q1 (<46.3, mm)	34/131 (26.0)	1.05 (0.61-1.82)	1.37 (0.63-2.97)	1.22 (0.55-2.70)
p-trend		0.8220	0.550	0.716
Premenopausal women				
Q4 (≥52.1, mm)	9/89 (10.1)	ref	ref	ref
Q3 (49.7-52.0, mm)	10/90 (11.1)	1.11 (0.43-2.88)	1.48 (0.53-4.14)	1.55 (0.55-4.36)
Q2 (46.8-49.7, mm)	13/86 (15.1)	1.58 (0.64-3.92)	2.32 (0.82-6.53)	2.48 (0.87-7.06)
Q1 (<46.8, mm)	9/86 (10.5)	1.04 (0.39-2.76)	2.22 (0.66-7.52)	2.49 (0.72-8.62)
p-trend		0.9872	0. 263	0.211
Postmenopausal women				
Q4 (≥50.8, mm)	28/159 (17.6)	ref	Ref	ref
Q3 (48.0-50.7, mm)	36/160 (22.5)	1.36 (0.78-2.36)	1.56 (0.85-2.85)	1.58 (0.86-2.91)
Q2 (45.3-48.0, mm)	41/158 (26.0)	1.64 (0.95-2.82)	**2.45 (1.30-4.62)**	**2.44 (1.29-4.63)**
Q1 (<45.3, mm)	47/157 (29.9)	**2.00 (1.17-3.40)**	**2.86 (1.46-5.61)**	**2.80 (1.42-5.52)**
p-trend		**0.033**	**0.008**	**0.012**

Model 1 analysis were adjusted covariates: Baseline age, BMI, waist circumference, IMT and follow-up period

Model 2 analysis were adjusted covariates: Baseline age, BMI, waist circumference, IMT, follow-up period, systolic BP, total cholesterol/HDL-C ratio, alcohol intake, and regular exercise

7. Association between thigh circumference and CIMT thickening according to baseline characteristics among baseline without CIMT thickening

Figure 3 shows the results of stratified analysis for baseline characteristics in relation to CIMT thickening per 5 cm decrease of thigh circumference among the baseline without CIMT thickening. The baseline characteristics were associated with CIMT thickening per 5 cm decrease of thigh circumference in the postmenopausal women (OR = 1.74, 95% CI = 1.28–2.35), with stronger associations than those in the men and premenopausal women. In addition, postmenopausal women appeared to have a better occurrence among never smokers (OR = 1.72, 95% CI = 1.27–2.34) and non-exercise (OR = 1.85, 95% CI = 1.27–2.68) even after adjusting for all potential confounding variables.



Adjusted for baseline age, BMI, waist circumference, CIMT, follow-up period, systolic BP, total-C/HDL-C ratio, alcohol intake and regular exercise

Figure 3. Prospective association between baseline thigh circumference and CIMT thickening at follow-up according to baseline characteristics (People with CIMT thickening < 1.0 mm at baseline)

IV. DISCUSSION

The current study investigated the association between thigh circumference and carotid IMT for different sexes and menopause status. Among postmenopausal women, we can see a significant inverse association between thigh circumference and CIMT even after adjusting for potential confounders. However, we cannot see a significant association between thigh circumference and CIMT in men or premenopausal women.

Thigh circumference was non-linearly associated with CIMT thickening. For those with thigh circumferences of less than 50.8 cm, the lower the thigh is, the higher their CIMT thickening among postmenopausal women. These findings resonate with the observations of other studies. In a study investigating the association of thigh circumference with early mortality and morbidity from coronary heart disease in the general population, it was noted that both men and women with thigh circumferences of less than 52 cm had about twice the risk of coronary heart disease, suggesting that smaller thighs are a disadvantage for health and survival (Heitmann and Frederiksen 2009). Previous studies have suggested a close association between lower body muscle mass, such as thigh muscle mass, thigh, and calf circumference and markers of atherosclerosis, such as cardio-ankle vascular index, carotid IMT, and ankle-brachial index (Ochi et al. 2010; Park et al. 2012; Tabara et al. 2009). These results indicate a significant association of decreased lower-body anthropometric parameters such as thigh circumference with the occurrence of CIMT thickening.

In this study, thigh circumference was associated with the occurrence of CIMT thickening in postmenopausal women, but not in men nor in premenopausal women. The sex differences and menopause status may explain, a previous publication used TromsØ study, Norway (Joakimsen et al. 1999). In their study, atherosclerosis occurs more frequently in men than in women. However, the sex gap in plaque prevalence is strongly influenced by age. The male-to-female ratio in prevalence peaks at age 45 to 49 years and then declines steadily, namely a linear prevalence peaked in men around age 45 to 49 and the age-related increase was blunted at advanced ages. But, in women there was linear accelerated increase in prevalence at age 50, the usual age at menopause. Also, the positive impact of premenopausal hormone status and the acceleration of atherosclerosis after menopause might explain this bimodal relation across genders (Arnal et al. 2007; Hsia et al. 2010; Touboul et al. 2007).

The increased risk of CVD in subjects with higher WTR is generally thought to be attributable to increased visceral fat mass (Kahn et al. 1996a; Kahn et al. 1996b; Terry et al. 1991). Indeed, we confirm a strong positive association of WTR with CIMT among postmenopausal women. A higher WTR, however, may also result from thigh circumference. Indeed, a higher thigh was found to be associated with an increased muscle mass in the legs and gluteal region after control for waist circumference (Kuk, Janiszewski and Ross 2007).

Body composition and large carotid artery properties may be influenced by behavioral characteristics such as smoking, alcohol consumption, and physical activity (Han et al. 1998). In this study, physical activity was positively associated with thigh circumference only in men (data not shown). Also, the associations between thigh circumference and CIMT thickening were not confounded by these lifestyle variables. Associations between estimates of thigh circumference and stiffness of the carotid IMT and CIMT thickening may, however, have been confounded and/or mediated by the other atherosclerosis risk factors considered.

Although the mechanism underlying the relationship of thigh circumference and carotid IMT is unknown, it was explained that less muscle mass and decreased peripheral fat mass are associated with atherosclerotic markers. One explanation could be a protective effect of a large amount of muscle mass on the occurrence of atherosclerosis. Although it is beyond the scope of the present study, recent studies have assessed the relationship between thigh muscle mass (using computed tomography) and carotid IMT showing a significant trend of increasing carotid IMT with decreasing thigh muscle cross-sectional area (Kato et al. 2010; Ochi et al. 2010). Reduced muscle mass could cause insulin resistance and physical decline, which could then promote atherosclerosis(Ryall, Schertzer and Lynch 2008). Growth hormone and insulin like growth factor system in myogenesis were associated with increased risk of acute myocardial infarction, ischaemic heart disease, stroke, coronary and carotid artery atherosclerosis (Colao 2008). A thyrotropin-releasing hormone receptor gene was associated with a lean body mass (Liu et al. 2009) and with atherosclerosis in the previous studies (Baxter and Webb 2009). According to these findings, there is a strong possibility that thigh muscle-mass loss and increased carotid IMT have potentially a common genetic background and share common pathological processes. On the other hand, the inverse relationship between carotid IMT thickening and increasing thigh circumference may also reflect a protective effect of increased peripheral fat mass. Indeed, several recent studies have reported peripheral fat mass to be negatively associated with several markers of atherosclerosis such as aortic calcifications, coronary angiography score, and arterial stiffness (Hara et al. 2004; Schouten et al. 2011; Tanko et al. 2003). Peripheral subcutaneous fat in the legs, compared with abdominal and, in particular visceral fat, has a low rate of lipolysis and is therefore more likely to effectively take up free fatty acids from the circulation and is less likely to release them readily (Arner 1995; Frayn 2002). The free fatty acid uptake in the peripheral subcutaneous may protect the liver and other organs from insulin resistance (Björntorp 1991; Carey 1998). We observed a significant inverse association between thigh circumference and atherosclerosis in postmenopausal women. In premenopausal women, the TG turnover rate is higher in visceral abdominal adipose tissue than in the femoral adipose tissue (Björntorp 1996). However, postmenopausal women seem to diminish this difference and estrogen replacement therapy restores according to the less lower body muscle mass and decreased peripheral fat mass. Peripheral fat mass showed an inverse correlation with aortic calcification, a direct measure of atherosclerosis (Hara et al. 2004; Tanko et al. 2003).

This study has strengths and limitations. First, the strengths include the prospectively collected data from community based individuals and the availability of carefully performed measures of subclinical atherosclerosis before the onset of stroke. Second, as far as we know, this study is the first study to examine the relationship between thigh circumference and carotid IMT in a general Korean population. Finally, this study conducted analyses with adjustment for potential confounders including age, BMI, SBP, total cholesterol, total cholesterol/HDL-C ratio, alcohol intake, and regular exercise. There are also limitations to be discussed. First, this study did not measure thigh muscle area and did not consider muscle quality, such as muscle strength. Muscle strength has been shown to be more relevant to functional alteration than muscle mass in several studies(Hughes et al. 2001). Second, more detailed thigh muscle and muscular lipid content assessed using computed tomography (CT), biopsy, and magnetic resonance spectroscopy were not measured in this study. In previous studies, it was reported that altered lipid partitioning within muscle was independently associated with carotid atherosclerosis (Kim et al. 2009). But, CT or magnetic resonance spectroscopy is expensive, therefore these are not suitable as a screening test. On the other hand, thigh circumference is a crude index of muscle mass and peripheral subcutaneous fat because thigh circumference reflects body muscle mass and peripheral subcutaneous fat (Heitmann and Frederiksen 2009; Kwon et al. 2011); these measurements are noninvasive and easily applicable and they are more suitable as screening tools. Third, this study recruited only voluntary participants. This might cause selection bias and not completely represent the whole geriatric population in Korea. Technical limitations to measurement (intra- and inter-observer variation) are also recognized. Finally, it may not be appropriate to generalize the study to another ethnic or age group because the study was conducted with Koreans recruited from a single rural community.

V. CONCLUSIONS

The present study reports that carotid IMT thickening showed significant increased frequency in subjects with a low thigh circumference independently of atherosclerosis risk factors and abdominal obesity indices among postmenopausal women. These results suggest that thigh circumference is a determinant of carotid IMT thickening independent of traditional risk factors. Also, it suggest that measure of thigh circumference might be a new anthropometric marker of early identification of individuals at an increased risk of atherosclerosis. Further, longitudinal studies should also test the association of thigh circumference with progression and incidence of atherosclerosis.

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ABSTRACT (IN KOREAN)

허벅지 둘레와 경동맥 내중막 비후의 관련성

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서론: 비만은 죽상경화증의 병인에 관련성이 있다고 보고되고 있다. 기존 선행 연구들에서 체질량지수 또는 복부비만과 관련되어 있는 허리둘레, 엉덩이둘레, 허리와 엉덩이둘레의 비 및 허리와 허벅지둘레의 비가 죽상경화증과 관련 있다는 연구들은 많이 진행되어 있지만 허벅지둘레와 같은 하체의 비만 지표와 죽상경화증의 연구는 많이 알려져 있지 않다. 따라서 이 연구는 허벅지 둘레와 죽상경화증 조기 표시자인 경동맥 내중막 두께의 관련성을 평가하고자 하였다.

방법: 이 연구는 2006-2011 년 4,899 명을 대상으로 강화도에서 진행되는 지역 기반 전향적 코호트 연구로, 평균 2.6 년의 추적조사기간에 걸쳐 재조사가 된 2,404 명이 연구의 대상자이다. 기초조사에서 뇌졸중, 협심증 및 암을

진단받았거나 신체계측지표 및 혈액이 채취 되지 않은 393 명을 제외한 2,011 명 (남자: 779 명, 폐경전여성: 393 명, 폐경후여성: 839 명)을 대상자로 한하였다. 경동맥 내중막 두께는 초음파(Aloka, Japan)을 이용하여 최대값(CIMT)을 측정하였고, 경동맥 내중막 비후는 CIMT 가 1.0mm 보다 큰 경우로 정의하였다. 허벅지둘레 와 경동맥 내중막 두께와의 독립적인 연관성은 단면 분석과 전향적 분석으로 성별 및 폐경 유무에 따른 선형회귀분석과 로지스틱 회귀분석으로 평가하였다.

결과: 기초조사의 허벅지 둘레는 경동맥 내중막 두께의 변화량과 잠재적 혼란변수인 연령, 체질량지수, 허리둘레, 수축기혈압, 총 콜레스테롤과 고밀도 지단백 콜레스테롤의 비, 음주 여부, 운동 여부, 추적조사기간을 보정한 후 폐경전 여자 (Standardized β for CIMT = -0.154, $p = 0.013$)와 폐경후 여자 (Standardized β for CIMT = -0.153, $p < 0.001$)에서 통계적으로 유의한 음의 관련성을 보였다. 그러나 남자에서는 이러한 관련성을 확인할 수 없었다. 기초조사의 경동맥 내중막 비후가 없었던 대상자 중 폐경후 여자에서 잠재적 혼란변수를 보정한 후 허벅지 둘레가 5 cm 감소할 때마다 경동맥 내중막 비후를 가질 위험은 1.74 배 (95% CI = 1.28 - 2.35)증가하였고 4 분위의 범주형 분석에서도 음의 경향성(각각 OR = 1.58, 2.44 and 2.80; p for trend = 0.012)을 보였다. 하지만 남자와 폐경전 여자에서는 이러한 관련성 및 경향성을 확인할 수 없었다.

고찰: 이 연구에서는 폐경후 여자에서 낮은 허벅지 둘레가 경동맥 내중막 비후와 관련성이 있었다. 이는 허벅지 둘레가 기존의 죽상경화증 위험요인 및 복부비만지표들과 독립적이며 죽상경화증 발생위험의 새로운 신체계측지표로 이용할 수 있다는 것이다. 추후 허벅지 둘레와 죽상경화증의 기전 및 발생에 대한 장기적 연구가 필요하다.

핵심되는 말: 허벅지 둘레, 경동맥 내중막 두께, 죽상경화증, 폐경